ORSZÁGOS FORDÍTÓ ÉS FORDÍTÁSHITELESÍTŐ IRODA

Hungarian National Office for Translations and Attestations
Ungarische Amtsstelle für Übersetzungen und Beglaubigungen
Венгерское Государственное Бюро Переводов и Заверений
Bureau National Hongrois de Traductions et de Légalisations

BUDAPEST

Translation from Hungarian

---------- THE REPUBLIC OF HUNGARY ----------

---------- **CERTIFICATE OF PRIORITY** ----------

Case No.: P0103055 ----------

The Hungarian Patent Office hereby certifies that Richter Gedeon Vegyészeti Gyár Rt. /Budapest/ filed a patent application in Hungary on 24th July, 2001, under registration No. 32793/01 for its invention entitled "New carboxylic acid-amide derivatives, the processes of manufcture, pharmaceutical preparations containing". ----------

The copy attached is in full conformity with the Annex filed simultaneously with the Application. -

Given at Budapest, this 20th day of November, in the year 2003. ----------

Certified true copy. ----------

illegible signature ----------

(SZABÓ Emília, Deputy Head of Patent Department) -

The Hungarian Patent Office certifies in this Priority certificate that the said applicant(s) filed a patent application at the specified date under the indicated title, application number and registration number. The attached photocopy is a true copy of specification filed with the application. ----------

L.S.: Hungarian Patent Office----------

Sz. 77734 /19 03 OFFICE

Hitelesen bizonyítom, hogy ez a fordítás
a fent idézett magyar
szöveggel
nyelvű
szövegnek részével
mindenben megegyezik.

2003 DEC. - 3

Budapest, 19

Az Országos Fordító és Fordításhitelesítő Iroda igazgatója

No. 77734 /19 03

The Hungarian National Office for Translations and Attestations hereby officially certifies that the above translation is in full conformity with the (attached) original passage (s) marked in the (attached) original.

Budapest 03. 12. /19 03

for the Director

ORSZÁGOS FORDÍTÓ ÉS FORDÍTÁSHITELESÍTŐ IRODA Budapest

HUNGARIAN NATIONAL OFFICE FOR TRANSLATIONS AND ATTESTATIONS Budapest

ILLETÉK 100 FORINT

ILLETÉK 100 FORINT

ILLETÉK 100 FORINT

MAGYAR KÖZTÁRSASÁG

ELSŐBBSÉGI TANÚSÍTVÁNY

Ügyszám: P0103055

A Magyar Szabadalmi Hivatal tanúsítja, hogy

Richter Gedeon Vegyészeti Gyár Rt., Budapest,

Magyarországon

2001. 07. 24. napján 32793/01 iktatószám alatt,

Új karbonsavamidszármazékok, eljárás az előállításukra, ezeket tartalmazó gyógyszerkészítmények és alkalmazásuk

című találmányt jelentett be szabadalmazásra.

Az idefűzött másolat a bejelentéssel egyidejűleg benyújtott melléklettel mindenben megegyezik.

Budapest, 2003. év 11. hó 20. napján

A kiadmány hiteléül: Szabó Emilné osztályvezető-helyettes

The Hungarian Patent Office certifies in this priority certificate that the said applicant(s) filed a patent application at the specified date under the indicated title, application number and registration number. The attached photocopy is a true copy of specification filed with the application.

New carboxylic acid amide compounds

Inventors:

dr. DOMÁNY György,	1022 Budapest, Bimbó u. 114/A.,	19 %,
HORVÁTH Csilla,	1105 Budapest, Dér u. 42. 3/14.,	17 %,
dr. FARKAS Sándor,	1103 Budapest, Olajliget u. 42.,	16 %,
BARTÁNÉ dr. Szalai Gizella,	1162 Budapest, Avarszállás u. 38.,	15 %,
dr. NAGY József,	1138 Budapest, Váci út 136/A 8.em. 39.,	9 %,
KOLOK Sándor,	1195 Budapest, Nagysándor József u. 8. I/4.,	8 %,
KOVÁCSNÉ dr. Bozó Éva,	1102 Budapest, Liget u. 40.	8 %,
BORZA István,	1186 Budapest, Margó Tivadar u. 218.,	8 %.

Applicant: Gedeon Richter Ltd, Budapest, Hungary

The invention relates to new carboxylic acid amide derivatives which are antagonists of NMDA receptor or are intermediates for preparing thereof.

Background of the invention.

N-methyl-D-aspartate (NMDA) receptors are ligand-gated cation-channels embedded in the cell membranes of neurons. Overactivation of NMDA receptors by glutamate, their natural ligand, can lead to calcium overload of cells. This triggers a cascade of intracellular events that alters the cell function and ultimately may lead to death of neurons [TINS, **10**, 299-302 (1987)]. Antagonists of the NMDA receptors may be used for treating many disorders that are accompanied with excess release of glutamate, the main excitatory neurotransmitter in the central nervous system.

The knowledge on the NMDA receptor structure, function and pharmacology has expanded owing to recent achievements of the molecular biology. The NMDA receptors are heteromeric assemblies built up from at least one NR1 subunit and at least one of the four different NR2 subunits (NR2A-D). Both spatial distributions in the CNS and the pharmacological sensitivity of NMDA receptors built up from various NR2 subunits are different. Particularly interesting of these is the NR2B subunit due to its restricted distribution (highest densities in the forebrain and substantia gelatinosa of the spinal cord). Compounds selective for this subtype are available [Curr. Pharm. Des., **5**, 381-404 (1999)] and have been proved to be effective in animal models of stroke [Stroke, **28**, 2244-2251 (1997)], traumatic brain injury [Brain Res., **792**, 291-298 (1998)], Parkinson's disease [Exp. Neurol., **163**, 239-243

(2000)], neuropathic and inflammatory pain [Neuropharmacology, **38**, 611-623 (1999)]. Moreover, NR2B subtype selective antagonists of NMDA receptors are expected to possess little or no untoward side effects that are typically caused by the non-selective antagonists of NMDA receptors, namely psychotomimetic effects such as dizziness, headache, hallucinations, dysphoria and disturbances of cognitive and motor function.

NR2B subtype selective NMDA antagonism can be achieved with compounds that specifically bind to, and act on, an allosteric modulatory site of the NR2B subunit containing receptors. This binding site can be characterised by displacement (binding) studies with specific radioligands, such as [^{125}I]-ifenprodil [J.Neurochem., **61**, 120-126 (1993)] or [^{3}H]-Ro 25,6981 [J. Neurochem., **70**, 2147-2155 (1998)]. Since ifenprodil was the first, though not sufficiently specific, known ligand of this receptor, it has also been termed ifenprodil binding site.

Close stucture analogs of the carboxylic acid amide derivatives of formula (I) are known from the literature.

The Florida Center for Heterocyclic Compounds [Department of Chemistry, University of Florida, P O Box 117200, Gainesville, FL, 32611-7200, USA] provides milligram quantities of three compounds of formula (I) for biological testing: N-(4-bromophenyl)-4-(phenylmethyl)-1-piperidineacetamide, 4-[[oxo[4-(phenylmethyl)-1-piperidinyl]acetyl]amino]benzoic acid and 4-[[oxo[4-(phenylmethyl)-1-piperidinyl]acetyl]amino]benzoic acid ethyl ester.

Oxo-ethylamino derivatives are described as intermediates for thrombin inhibitors [Bioorg. Med. Chem. Letters, **9**, 925. (1999)]. The publication does not describe NMDA receptor antagonist effect.

N-(4-Benzoylphenyl)-4-(phenylmethyl)-1-piperidineacetamide is mentioned in patent No. US 6,048,900 as selective neuropeptide Y receptor antagonist.

N-(2-Formyl-6-methylphenyl)-4-(phenylmethyl-1-piperidineacetamide is described in patent No. AU 639529 as intermediate for carbostyril derivative which is useful as antiarrhythmics.

Aminoacetarylides are also known [Rev. Chim. (Bucharest), **33(7)**, 601. (1982); CA **97**:174467a] as local anesthetic and antifibrillatory agents.

Piperidine derivatives and analogues substituted with phenols or phenol equivalents having NR2B selective NMDA antagonist activity are described in international patent applications WO90/14087, WO90/14088, WO97/23202, WO97/23214, WO97/23215, WO97/23216, WO97/23458, WO99/21539, WO2000/25109, EP648,744 and in US 5,436,255. Compounds containing 2-benzoxazolinone substructure with the same biological activity are

described in international patent applications WO98/18793 and WO2000/00197. Other NR2B selective NMDA antagonists having condensed heterocyclic structures are described in WO2001/30330, WO2001/32171, WO2001/32174, WO2001/32177, WO2001/32179, WO2001/32615, WO2001/32634.

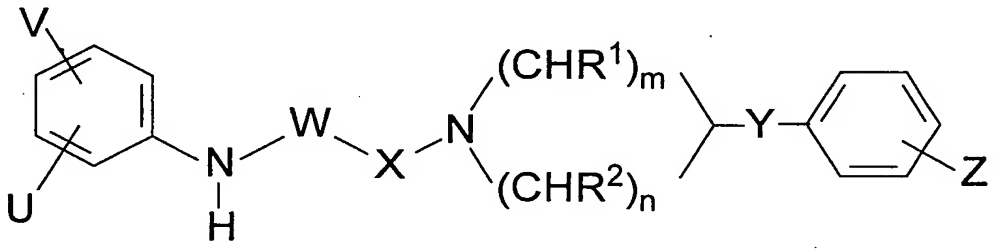
However, there continues to be a need for novel NMDA antagonists that target the NR2B receptor.

Summary of the invention

Surprisingly it was found that the new carboxylic acid amide derivatives of formula (I) of the present invention are functional antagonists of NMDA receptors, which target the NMDA receptors primarily via binding to the ifenprodil binding site. Therefore, they are believed to be NR2B subtype specific antagonists.

Detailed description of the invention

The present invention relates therefore first to new carboxylic acid amide derivatives of formula (I)



(I)

- wherein

V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C_1-C_4 alkylamino optionally substituted by a halogen atom or halogen atoms , arylamino optionally substituted by a halogen atom or halogen atoms , aralkylamino optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C_1-C_4 alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C_1-C_4 alkyl-SO_2-NH-CH_2-, NH_2-$(CH_2)_{1-4}$-SO_2-NH-, NH_2-$(CH_2)_{1-4}$-(CO)-NH-, sulfamoyl [NH_2-SO_2-], formyl [-CHO], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, halogenmethyl, tetrazolyl group, or C_1-C_4 alkoxy, C_1-C_4

alkoxycarbonyl, C_1-C_6 alkanoyloxy, phenyl or C_1-C_4 alkoxy groups, optionally substituted by amino group, or

the neighboring V and U groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form a 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

W and X independently are carbonyl, methylene, -C(=NOH)-, -C(=NH)-, -CH(alkyl)- group - wherein alkyl is a C_1-C_4 alkyl group - with the restriction, that the meaning of W and X can not be methylene at the same time

Y is oxygen atom, as well as C_1-C_4 alkylene, C_1-C_4 alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)-, -CH_2O-, -CH(OH)-, -OCH_2- group, - wherein alkyl is a C_1-C_4 alkyl group -,

Z is hydrogen or halogen atom, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R^1 and R^2 independently are hydrogen atom or alkyl group, or R^1 and R^2 together form an optionally substituted C_1-C_3 bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time,

and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases with the proviso that

when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, W means -CO- group, X means -CH_2- group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, both of W and X mean -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxycarbonyl substituent.

Furthermore objects of the present invention are the pharmaceutical compositions containing carboxylic acid amide compounds of formula (I) or optical antipodes or racemates or the salts thereof as active ingredients.

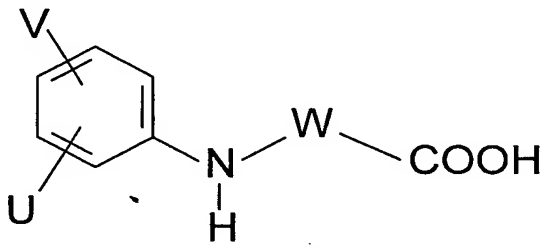
A further object of the invention are the processes for producing of carboxylic acid amide compounds of formula (I), and the pharmaceutical manufacture of medicaments containing these

compounds, as well as the process of treatments with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

The new carboxylic acid amide derivatives of formula (I) of the present invention are highly effective and selective antagonists of NMDA receptor, and moreover most of the compounds are selective antagonist of NR2B subtype of NMDA receptor.

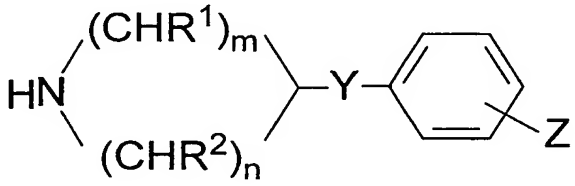
According to the invention the carboxylic acid amide compounds of formula (I) can be prepared by the following processes

a.) for producing of compounds of formula (I) having -CO- group in place of X - wherein the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (I) - a carboxylic acid of formula (II)



(II)

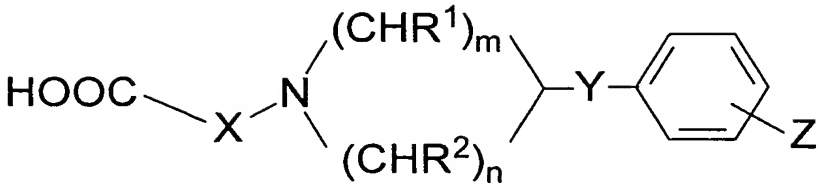
- wherein the meaning of U, V and W are as given for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (III)



(III)

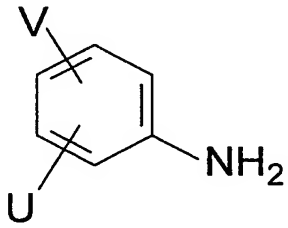
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (I) - , or

b.) for producing of compounds of formula (I) having -CO- group in place of W - wherein the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) - a carboxylic acid of formula (IV)



(IV)

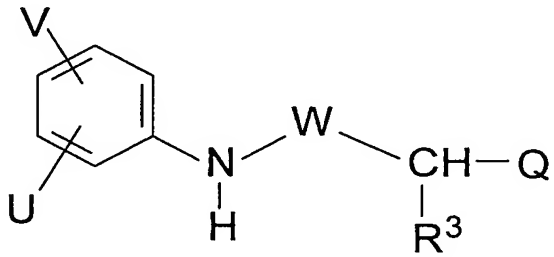
- wherein the meaning of X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (V)



(V)

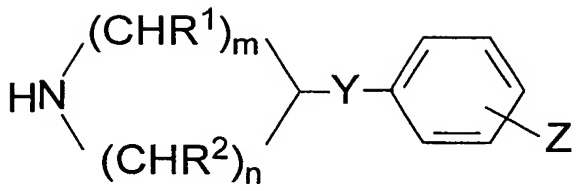
- wherein the meaning of U and V are as given before for the formula of (I) -, or

c.) for producing of compounds of formula (I) having $-CH_2-$ or -CH(-alkyl)- group in place of X - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VI)



(VI)

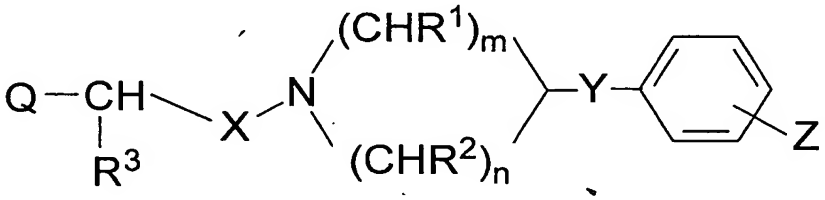
- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and U, V and W are as described above for the formula of (I) - is reacted with an amine of formula (III)



(III)

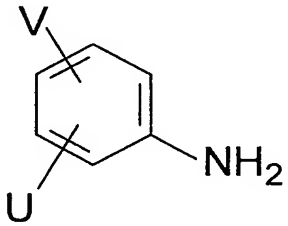
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (I) -, or

d.) for producing of compounds of formula (I) having $-CH_2-$ or -CH(-alkyl)- group in place of W - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VII)



(VII)

- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - is reacted with an amine of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) -,

and the obtained compounds of formula (I) - where R^1, R^2, Y, Z, U, V, X, W, n and m are as defined above - in given case are transformed into an other compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid

amide derivative of formula (I) can be transformed into a salt by treatment with a base and/or are resolved into their optical antipodes.

The amide bond formation is preferably carried out by preparing an active derivative from a carboxylic acid of formula (II) or (IV) which is reacted with an amine of formula (III) or (V) preferably in the presence of a base.

The transformation of a carboxylic acid into an active derivative can be carried out in situ during the amide bond formation in a proper solvent (for example dimethylformamide, acetonitrile, chlorinated hydrocarbons or hydrocarbons). The active derivatives can be acid chlorides (for example prepared from carboxylic acid with thionyl chloride), mixed anhydrides (for example prepared from carboxylic acid with isobutyl chloroformate in the presence of a base, e.g. triethylamine), active esters (for example prepared from carboxylic acid with hydroxybenztriazol and dicyclohexyl-carbodiimide or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) in the presence of a base e.g. triethylamine), acid azides (for example prepared from carboxylic acid hydrazide). The active derivatives can be prepared between room temperature and 0 °C. A proper amine of formula (III) or (V) is added as base or as a salt formed with inorganic acid to the so obtained solution or suspension in the presence of a base, for example triethylamine, needed for the liberation of the amine. The condensation reactions are followed by thin layer chromatography. The necessary reaction time is 6-20 h. The work-up of the reaction mixture can be carried out by different methods.

The amide bond formation is preferably carried out by refluxing in a proper solvent an amine of formula (III) or (V) with a halogen compound of formula (IV) or (VII) in the presence of an organic base (for example triethylamine, pyridine, piperidine) or an inorganic base (for example sodium carbonate or potassium carbonate) and sodium iodide. The proper solvent can be an aprotic solvent (for example toluene, chlorinated hydrocarbons) or a dipolar aprotic solvent (for example keton, acetonitrile or dimethylformamide). The reactions are followed by thin layer chromatography. The necessary reaction time is 20-50 h. The work-up of the reaction mixture also can be carried out by different methods.

When the reaction mixture is a suspension, the precipitate is filtered off, washed with water and/or with an organic solvent and recrystallized from a proper solvent to give the pure product. If the crystallization does not lead to the pure product, then column chromatography can be used for the purification of it. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. toluene/methanol, chloroform/methanol or toluene/acetone, as eluents. If the reaction mixture is a solution at the

end of the acylation or alkylation, it is concentrated, and the residue is crystallized or purified by column chromatography as described above. The structure of the products are determined by IR, NMR and mass spectrometry.

The obtained carboxylic acid amide derivatives of formula (I) – independently from the method of preparation – in given case can be transformed into an other compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (I) can be transformed into a salt by treatment with a base.

For example cleaving the methyl and benzyl groups from methoxy and benzyloxy groups, which stands for U,V and Z, leads to phenol derivatives. The removal of the benzyl group can be carried out for example with catalytic hydrogenation or with hydrogen bromide in acetic acid solution, the cleavage of methyl group can be carried out with boron tribromide in dichloromethane solution. The compounds of formula (I) containing free phenolic hydroxy group can be transformed into acyloxy or sulfoxy derivatives with different acylating or sulfonylating agents. The reactions are carried out at room temperature in chlorinated hydrocarbons using acid chloride or acid anhydride as acylating agent in the presence of a base (for example triethylamine or sodium carbonate). The carboxylic acid amide derivatives of formula (I) containing a nitro group (I) can be transformed into amines by catalytic hydrogenation and the amines can be further reacted to give acid amides as described for the acylation of phenolic hydroxy groups. Free hydroxy groups can be esterified by acid anhydrides or acid halogenides in the presence of a base.

The carboxylic acids of formula (II) or (IV), the primary or secondary amines of formula (III) or (V) and the halogene compounds of formula (VI) or (VII) are either commercially available or can be synthesized by different known methods. The syntheses of some commercially not available carboxylic acids of formula (II) or (IV) or halogen compounds of (VI) or (VII) are described in the Examples. Following these procedures the other commercially not available carboxylic acids of formula (II) or (IV) or halogen compounds of formula (VI) or (VII) can also be prepared.

Experimental protocols

Assessing the functional NMDA antagonist potency of compounds in primary cultures of rat cortical neurons based on measuring the intracellular calcium concentration using a fluorimeter plate reader

It is known that during postnatal development the subunit composition of neuronal NMDA receptors is changing. Similar change has been detected in neuronal cell cultures [Eur. J. Neurosci., **10**, 1704-1715 (1998)]. According to data in the literature and to our own immunocytochemical examinations neuronal cells cultured for 4-7 days *in vitro* predominantly express the NR2B subunit, together with NR1 subunit. Therefore, functional test of NMDA antagonism in these cells reflects mainly an action on NR2B subunit containing receptors. Since NMDA receptors are known to be permeable to calcium ions upon excitation, the extent of NMDA receptor activation, and its inhibition by functional antagonists can be characterised by measuring the rise in the intracellular calcium concentration following agonist (NMDA) application onto the cells. Since there is very high sequence homology between rat and human NMDA receptors (99, 95, 97 % for NR1, NR2A, and NR2B subunits, respectively), it is believed that there is little, if any, difference in their pharmacological sensitivity. Hence, results obtained with (cloned or native) rat NMDA receptors may be well extrapolated to the human ones.

The intracellular calcium measurements are carried out on primary neocortical cell cultures derived from 17 day old Charles River rat embryos [for the details on the preparation of neocortical cell culture see Johnson, M.I.; Bunge, R.P. (1992): Primary cell cultures of peripheral and central neurons and glia. In: Protocols for Neural Cell Culture, eds: Fedoroff, S.; Richardson A., The Humana Press Inc., 13-38.] After isolation, the cells are plated onto standard 96-well microplates and the cultures are maintained in an atmosphere of 95 % air-5 % CO_2 at 37 °C until testing.

The cultures are used for the intracellular calcium measurements after 4-7 days in vitro. The cells are loaded with a fluorescent Ca^{2+}-sensitive dye, Fluo-4/AM (2-2.5 μM) prior to testing. Loading is stopped by washing twice with the solution used also during the measurement (140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 5 mM HEPES [4-(2-hydroxyethyl)-1-piperazineethane-sulfonic acid], 5 mM HEPES-Na, 20 mM glucose, 10 μM glycine, pH=7.4). Then the test compound dissolved in the above solution (90 μl/well) is added. Intracellular calcium measurements are carried out with a plate reader fluorimeter. A rise is induced by application of 40 μM NMDA in Fluo-4-fluorescence that reflects the intracellular calcium concentration. Inhibitory potency of the test compound is assessed by measuring the reduction in the calcium elevation in the presence of different concentrations of the compound. After the measurement, a standard calibration procedure [Meth. Cell. Biol., **40**, 155-181 (1994)] is applied to convert the fluorescence data to calcium concentration values.

Inhibitory potency of a compound at a single concentration point is expressed as percent inhibition of the control NMDA response. Sigmoidal concentration-inhibition curves are fitted over the data and IC_{50} values are defined as the concentration that produces half of the maximal inhibition that could be achieved with the compound. Mean IC_{50} values are derived from at least three independent experiments.

Determining binding of compounds to NR2B subunit by [^{3}H]-Ro 25,6981 binding assay

The method is essentially similar to that described by Mutel et al. [J. Neurochem., **70**, 2147-2155 (1998)] except for incubation temperature and radioligand concentration. Briefly, membranes are isolated from the forebrain of male Wistar rats. They are incubated in the presence and absence of test compound for 2 h at room temperature. Non-specific binding is determined using 10 μM Ro-25,6981, and is typically less than 7% of the total binding. The applied radioligand (^{3}H-Ro-25,6981) concentration is 4 nM. IC_{50} values (50 % inhibitory concentrations) are determined from sigmoidal fits plotted over concentration-displacement curves.

The biological activity of the compounds

IC_{50} values for selected examples of compounds of this invention in the functional NMDA antagonism and in the binding tests are listed in Table 1 and compared to those determined for the most potent known reference compounds.

The compounds of this invention exhibit IC_{50} values of less than 50 μM in the functional NMDA antagonism and in the binding tests. Thus the compounds and pharmaceutical compositions of this invention are NR2B subtype specific NMDA antagonists. Some of the compounds have superior potency compared to the known reference compounds (see Table 1).

Table 1

NMDA antagonist/binding activity of compounds on native neurons/neuronal membranes from rats

ID code of compound (No. of example)	NMDA IC_{50} [μM]	Ro-binding IC_{50} [μM]	Code of reference compound	NMDA IC_{50} [μM]	Ro-binding IC_{50} [μM]
70001623 (2)	0.0007	0.0047	CI-1041	0.0066	0.004
70001824 (11)	0.0014	0.0044	Co-101244	0.023	0.0033
70001861 (13)	0.0024	0.0055	EMD 95885	0.035	0.0072
70001620 (3)	0.0032	0.018	CP 101,606	0.041	0.0084
70001825 (12)	0.006	0.0017	Co-111103	0.060	0.0084

70001863 (14)	0.048	0.091	Ro 25.6981	0.159	0.0059
70001844 (28)	0.113	0.214	ifenprodil	0.483	0.096
70001712 (5)	0.164	0.029			
70001843 (27)	0.533	0.972			
70001990 (17)	1.01	0.614			
70001894 (29)	1.33	0.121			
70001759 (7)	4.71	>30			

NMDA IC_{50}: IC_{50} determined by the intracellular Ca^{2+}-concentartion assay on cortical neurons

Ro-binding IC_{50}: IC_{50} determined by the [^{3}H]-Ro 25,6981 binding assay on rat cerebral membranes

The reference compounds are as follows:

CI-1041: 6-{2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanesulfinyl}-3*H*-benzooxazol-2-one

Co 101244: 1-[2-(4-hydroxyphenoxy)ethyl]-4-hydroxy-4-(4-methylbenzyl)piperidine

EMD 95885: 6-[3-(4-fluorobenzyl)piperidine-1-yl]propionyl]-2,3-dihydro-benzoxazol-2-on

CP-101,606: (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidine-1-yl)-1-propanol

Co-111103: 1-[2-(4-hydroxyphenoxy)ethyl]-4-(4-fluorobenzyl)piperidine

Ro 256981: R-(R*,S*)-1-(4-hydroxyphenyl)-2-methyl-3-[4-(phenylmethyl)piperidin-1-yl]-1-propanol.

Ifenprodil: *erythro*-2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-1-propanol

Disorders which may be beneficially treated with NMDA antagonists include traumatic injury of brain [Neurol. Res., **21**, 330-338 (1999)] or spinal cord [Eur. J. Pharmacol., **175**, 165-74 (1990)], human immunodeficiency virus (HIV) related neuronal injury [Annu. Rev. Pharmacol. Toxicol., **1998**; 38159-77], amyotrophic lateral sclerosis [Neurol. Res., **21**, 309-12 (1999)], tolerance and/or dependence to opioid treatment of pain [Brain. Res., **731**, 171-181 (1996)], withdrawal syndromes of e.g. alcohol, opioids or cocaine [Drug and Alcohol Depend., **59**, 1-15 (2000)], muscular spasm [Neurosci. Lett., **73**, 143-148 (1987)], dementia of various origins [Expert Opin. Investig. Drugs, **9**, 1397-406 (2000)]. An NMDA antagonist may also be useful to treat cerebral ischemia of any origin (e.g. stroke, heart surgery), chronic neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, pain (e.g. posttraumatic or postoperative) and chronic pain states, such as neuropathic pain or cancer related pain, epilepsy, anxiety, depression, migraine, psychosis, hypoglycemia, degenerative disorders of the retina (e.g. CMV retinitis), glaucoma, asthma, tinnitus,

aminoglycoside antibiotic-induced hearing loss [Drug News Perspect 11, 523-569 (1998) and WO 00/00197 international patent application].

Accordingly, effective amounts of the compounds of the invention may be beneficially used for the treatment of traumatic injury of brain or spinal cord, human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis, tolerance and/or dependence to opioid treatment of pain, withdrawal syndromes of e.g. alcohol, opioids or cocaine, ischemic CNS disorders, chronic neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, pain and chronic pain states, such as neuropathic pain or cancer related pain, epilepsy, anxiety, depression, migraine, psychosis, muscular spasm, dementia of various origin, hypoglycemia, degenerative disorders of the retina, glaucoma, asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss.

The compounds of the invention as well as their pharmaceutically acceptable salts can be used as such or suitably in the form of pharmaceutical compositions. These compositions (drugs) can be in solid, liquid or semiliquid form and pharmaceutical adjuvant and auxiliary materials can be added, which are commonly used in practice, such as carriers, excipients, diluents, stabilizers, wetting or emulsifying agents, pH- and osmotic pressure-influencing, flavoring or aromatizing, as well as formulation-promoting or formulation-providing additives.

The dosage required to exert the therapeutical effect can vary within wide limits and will be fitted to the individual requirements in each of the particular cases, depending on the stage of the disease, the condition and the bodyweight of the patient to be treated, as well as the sensitivity of the patient against the active ingredient, route of administration and number of daily treatments. The actual dose of the active ingredient to be used can safely be determined by the attending physician skilled in the art in the knowledge of the patient to be treated.

The pharmaceutical compositions containing the active ingredient according to the present invention usually contain 0.01 to 100 mg of active ingredient in a single dosage unit. It is, of course possible that the amount of the active ingredient in some compositions exceeds the upper or lower limits defined above.

The solid forms of the pharmaceutical compositions can be for example tablets, dragées, capsules, pills or lyophilized powder ampoules useful for the preparation of injections. Liquid compositions are the injectable and infusable compositions, fluid medicines, packing fluids and drops. Semiliquid compositions can be ointments, balsams, creams, shaking mixtures and suppositories.

For the sake of a simple administration it is suitable if the pharmaceutical compositions comprise dosage units containing the amount of the active ingredient to be administered once, or a few multiples or a half, third or fourth part thereof. Such dosage units are e.g. tablets, which can be powdered with grooves promoting the halving or quartering of the tablet in order to exactly administer the required amount of the active ingredient.

Tablets can be coated with an acid-soluble layer in order to assure the release of the active ingredient content after leaving the stomach. Such tablets are enteric-coated. A similar effect can be achieved also by encapsulating the active ingredient.

The pharmaceutical compositions for oral administration can contain e.g. lactose or starch as excipients, sodium carboxymethylcellulose, methylcellulose, polyvinyl pyrrolidine or starch paste as binders or granulating agents. Potato starch or microcrystalline cellulose is added as disintegration agents, but ultraamylopectin or formaldehyde casein can also be used. Talcum, colloidic silicic acid, stearin, calcium or magnesium stearate can be used as antiadhesive and lubricants.

The tablet can be manufactured for example by wet granulation, followed by pressing. The mixed active ingredients and excipients, as well as in given case part of the disintegrants are granulated with an aqueous, alcoholic or aqueous alcoholic solution of the binders in an appropriate equipment, then the granulate is dried. The other disintegrants, lubricants and antiadhesive agents are added to the dried granulate, and the mixture is pressed to a tablet. In given case the tablets are made with halving groove to ease the administration.

The tablets can be made directly from the mixture of the active ingredient and the proper auxiliaries by pressing. In given case, the tablets can be coated by using additives commonly used in the pharmaceutical practice, for example stabilizers, flavoring, coloring agents, such as sugar, cellulose derivatives (methyl- or ethylcellulose, sodium carboxymethylcellulose, etc), polyvinyl pyrrolidone, calcium phosphate, calcium carbonate, food coloring agents, food laces, aroma agents, iron oxide pigments, etc. In the case of capsules the mixture of the active ingredient and the auxiliaries is filled into capsules.

Liquid oral compositions, for example suspensions, syrups, elixirs can be made by using water, glycols, oils, alcohols, coloring and flavoring agents.

For rectal administration the composition is formulated in suppositories or clysters. The suppository can contain beside the active ingredient a carrier, so called adeps pro suppository. Carriers can be vegetable oils, such as hydrogenated vegetable oils, triglycerides of C12-C18

fatty acids (preferably the carriers under the trade name Witepsol). The active ingredient is homogeneously mixed with the melted adeps pro suppository and the suppositories are moulded.

For parenteral administration the composition is formulated as injection solution. For manufacturing the injection solution the active ingredients are dissolved in distilled water and/or in different organic solvents, such as glycolethers, in given case in the presence of solubilizers, for example polioxyethylensorbitane-monolaurate, -monooleate, or monostearate (Tween 20, Tween 60, Tween 80). The injection solution can also contain different auxiliaries, such as conserving agents, for example ethylendiamine tetraacetate, as well as pH adjusting agents and buffers and in given case local anaesthetic, e.g. lidocain. The injection solution containing the active ingredient of the invention is filtered before it is filled into ampoules, and it is sterilized after filling.

If the active ingredient is hygroscopic, then it can be stabilized by liophylization.

The following examples illustrate the invention without the intention of limitation anyway.

Example 1

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5--yl)acetamide (45 70001598)

1a) [4-(4-Fluorobenzyl)piperidine-1-yl]oxoacetic acid ethyl ester

To a stirred solution of 2.3 g (10 mmol) of 4-(4-fluorobenzyl)piperidine hydrochloride [J. Med. Chem., **35**, 4903. (1992)] and 4.5 ml (32 mmol) of triethylamine in 80 ml of chloroform 2.5 ml (22 mmol) of ethyl oxalyl chloride in 20 ml of chloroform is added dropwise below 10 °C, and the reaction mixture is stirred at room temperature for 10 h. Then 50 ml of 8 % sodium hydrogen carbonate solution is added to the mixture, the organic layer is separated and the water phase is extracted three times with 25 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated, the residue is treated with diisopropil ether and the crystals are filtered to yield 2.1 g (72 %) of the title compound. Mp.: 72-74 °C (diisopropil ether)

1b) [4-(4-Fluorobenzyl)piperidine-1-yl]oxoacetic acid

To a stirred solution of 1.91 g (6.5 mmol) of [(4-fluorobenzyl)piperidine-1-yl]oxoaceticacid ethyl ester in 15 ml of ethanol is added a solution of 1.18 g (21.1 mmol) of potassium hydroxide in 3 ml of water. The reaction mixture is stirred for 6 h and is cooled and is acidified with hydrochloric acid. The solid is collected, washed with water to yield 1.68. (97.4 %) g of the title compound. Mp.: 152-154 °C (ethanol-water)

1c) 2-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5--yl)acetamide

A mixture of 3.2 g (12 mmol) of [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid, 1.4 ml (10 mmol) of triethylamine, 1.5 g (10 mmol) of 5-amino-1,3-dihydro-indol-2-one [Tetrahedron, **24**, 1376. (1957)] 3.8 g (10 mmol) of HBTU [O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (Advanced Chem. Tech.)] and 100 ml of dimethylformamide is stirred at room temperature for 24 h. The reaction mixture is concentrated. Then 150 ml of 8 % sodium hydrogencarbonate solution and 150 ml of chloroform is added to the mixture. The organic layer is separated and the water phase is extracted three times with 25 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated and the residue is purified by column chromatography using Kieselgel 60 as adsorbent (Merck) and chloroform : methanol =19 :1 as eluent to yield 2.67 g (68 %) of the title compound. Mp.: 195-197 °C (diethylether)

Example 2

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide (45 70001623)

A mixture of 2.5 g (9.6 mmol) of [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid (Example 1a), 1.1 ml (8 mmol) of triethylamine, 1.2 g (8 mmol) of 5-amino-1,3-dihydro-benzimidazol-2-one [J. Amer. Chem. Soc., **80,** 1657. (1958)] 3.03 g (8 mmol) of HBTU and 80 ml of dimethylformamide is stirred at room temperature for 24 h. The reaction mixture is concentrated, then 100 ml of 8 % sodium hydrogencarbonate solution is added. The precipitated product is filtered off and recrystallized from methanol to yield 1.51 g (48 %) of the title compound. Mp.: > 260 °C (methanol).

Example 3

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)acetamide (45 70001620)

The title compound is prepared from [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid (Example 1b) and 6-amino-3H –benzoxazol-2-one [J. Chem. Soc., 321. (1938)] according to the method described in Example 1c. Mp.: 224-227 °C (diethylether)

Example 4

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)acetamide (45 70001655)

4a) 2-Chloro-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)acetamide

To a stirred solution of 1.5 g (10 mmol) of 6-amino-3H-bezoxazol-2-one and 3.4 ml (24 mmol) of triethylamine in 90 ml of chloroform 2 ml (24 mmol) of chloroacetyl chloride in 20 ml of chloroform is added dropwise below 10 °C, and the reaction mixture is stirred at room temperature for 10 h. The reaction mixture is concentrated and to the residue is added 100 ml of 8 % sodium hydrogencarbonate solution. The precipitated product is filtered off, and washed with water to yield 1.76 g (78 %) of the title compound. Mp.: 228-231 °C (water)

4b) 2-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-l)acetamide

A mixture of 0.91 g (4 mmol) of 2-chloro-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)acetamide, 0.7 g (4 mmol) of sodium iodide, 1.2 ml (8 mmol) of triethylamine, 0.7 g (3 mmol) of 4-(4-fluorobenzyl)piperidine hydrochloride and 50 ml of acetonitrile is refluxed for 20 h. The reaction mixture is concentrated and to the residue 30 ml of water and 30 ml of chloroform is added. The organic layer is separated and the water phase is extracted three times with 10 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated and the

residue is purified by column chromatography using Kieselgel 60 adsorbent (Merck) and chloroform :methanol = 97 :3 as eluent to yield 0.3 g (26 %) of the title compound. Mp.: 232-234 °C (diethylether)

Example 5

2-(4-Benzylpiperidine-1-yl)-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide (45 70001712)

5a) 2-Chloro-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide

The title compound is prepared from 5-amino-1,3-dihydro-indol-2-one and chloroacetyl chloride according to the method described in Example 4a. Mp.: 166-170 °C (water)

5b) 2-(4-Benzylpiperidine-1-yl)-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide

A mixture of 0.9 g (4 mmol) of 2-chloro-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide, 0.7 g (4 mmol)of sodium iodide, 0.6 ml (4 mmol) of triethylamine, 0.53 ml (3 mmol) of 4-benzyl)piperidine and 50 ml of acetonitrile is refluxed for 20 h. The reaction mixture is concentrated and to the residue 30 ml of water and 30 ml of chloroform is added. The organic layer is separated and the water phase is extracted three times with 10 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated and the residue is treated with diethylether and the precipitated crystals are filtered off to yield 0.7 g (64 %) of the title compound. Mp.: 176-180 °C (diethylether)

Example 6

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide (45 70001758)

The title compound is prepared from 2-chloro-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide (Example 5a) and 4-(4-fluorobenzyl)piperidine hydrochloride according to the method described in Example 4b. Mp.: 178-180 °C (diethylether)

Example 7

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-5-yl)acetamide (45 70001759)

The title compound is prepared from 5-amino-3H-benzoxazole-2-one [J. Med. Chem., **10,** 408. (1967)] and [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid according to the method described in Example 2. Mp.: 226-231 °C (water)

Example 8

2-(4-Benzyl)piperidine-1-yl]-N-(4-cyanophenyl)-2-oxoacetamide (45 70001798)

8a) (4-Benzylpiperidine-1-yl)oxoaceticacid ethyl ester

The title compound is prepared from 4-benzylpiperidine and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil

8b) (4-Benzylpiperidine-1-yl)oxoaceticacid

The title compound is prepared from (4-benzylpiperidine-1-yl)oxoaceticacid ethyl ester according to the method described in Example 1b. Mp.: 109-112 °C (ethanol-water)

8c) 2-(4-Benzylpiperidine-1-yl)-N-(4-cyanophenyl)-2-oxoacetamide

The title compound is prepared from 4-aminobenzonitrile (Aldrich) and (4-benzylpiperidine-1-yl)oxoacetic acid according to the method described in Example 2. Mp.: 166-169 °C (diethylether)

Example 9

2-(4-Benzylpiperidine-1-yl)-N-(4-cyanophenyl)acetamide (45 70001822)

The title compound is prepared from 2-chloro-N-(4-cyano-phenyl)acetamide [J. Org. Chem., **23**, 141. (1958)] and 4-benzylpiperidine according to the method described in Example 4b. Mp.: 120-124 °C (diethylether)

Example 10

2-(4-Benzylpiperidine-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide (45 70001823)

The title compound is prepared from (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8a) and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. Mp.: 115-118 °C (water)

Example 11

2-(4-Benzylpiperidine-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide (45 70001824)

The title compound is prepared from (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8a) and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example 2. Mp.: > 260 °C (water)

Example 12

2-(4-Benzylpiperidine-1-yl)-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)acetamide (45 70001825)

The title compound is prepared from 2-chloro-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)acetamide (Example 4a) and 4-benzylpiperidine according to the method described in Example 5b. Mp.: 210-212 °C (water)

Example 13

2-(4-Benzylpiperidine-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)acetamide (45 70001861)

The title compound is prepared from (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8b) and 6-amino-3H-benzoxazol-2-one according to the method described in Example 1c. Mp.:190-193 °C (diethylether)

Example 14

5-{2-[4-(4-Fluorobenzyl)piperidine-1-il]-2-oxoethylamino}-1,3-dihydro-benzimidazol-2-one (45 70001863)

14a) 2-Chloro-1-[4-(4-fluorobenzyl)piperidine-1-yl]ethanone

The title compound is prepared from 4-(4-fluorobenzyl)piperidine and chloroacetyl chloride according to the method described in Example 4a. Mp.: 85-87 °C (water)

14b) 5-{2-[4-(4-Fluorobenzyl)piperidine-1-il]-2-oxoethylamino}-1,3-dihidro-benzimidazol-2-one

The title compound is prepared from 2-chloro-1-[4-(4-fluorobenzyl)piperidine-1-yl]ethanone and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example 4b. Mp.: 249-251 °C (diethylether)

Example 15

6-{2-[4-(4-Fluorobenzyl)piperidine-1-il]-2-oxoethylamino}-3H-benzoxazol-2-one (45 70001944)

The title compound is prepared from 2-chloro-1-[4-(4-fluorobenzyl)piperidine-1-yl]ethanone (Example 14a) and 6-amino-3H-benzoxazol-2-one according to the method described in Example 4b. Mp.: 202-205 °C (diethylether)

Example 16

N-(4-Cyanophenyl)-2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxoacetamide (45 70001946)

The title compound is prepared from 4-aminobenzonitrile and [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid (Example 1b) according to the method described in Example 1c. Mp.: 167-169 °C (diethylether)

Example 17

2-(4-Benzylpiperidine-1-yl)-N-(3-methylsulfonylaminophenyl)-2-oxoacetamide 45 70001990

17a) N-(3-Nitrophenyl)oxalamic acid

The title compound is prepared from N-(3-nitrophenyl)oxalamic acid ethyl ester [J.Chem. Soc., **121,** 1501. (1922)] according to the method described in Example 1b. Mp.: > 270 °C (ethanol-water)

17b) 2-(4-benzylpiperidine-1-yl)-N-(3-nitro-phenyl)-2-oxoacetamide (45 70001862)

The title compound is prepared from N-(3-nitrophenyl)oxalamic acid and 4-benzylpiperidine according to the method described in Example 1c. Mp.: 138-140 °C (diethylether)

17c) N-(3-aminophenyl)-2-(4-benzylpiperidine-1-yl)-2-oxoacetamide (45 70001945)

A mixture of 1.8 g (4.9 mmol) of 2-(4-benzylpiperidine-1-yl)-N-(3-nitro-phenyl)-2-oxoacetamide, 50 ml of dimethylformamide, 0.5 g of 10 % Pd/C catalyst is hydrogenated for 2 h. The catalyst is filtered off, washed with dimethylformamide and the filtrate is concentrated. The residue is treated with diethylether and the precipitated crystals are filtered off to yield 1.41 g (83 %) of the title compound. Mp.: 103-105 °C (diethylether)

17d) 2-(4-Benzylpiperidine-1-yl)-N-(3-methylsulfonylaminophenyl)-2-oxoacetamide

To a stirred solution of 0.34 g (1 mmol) of N-(3-aminophenyl)-2-(4-benzylpiperidine-1-yl)-2-oxoacetamide and 0.16 ml (2 mmol) of pyridine in 10 ml of dichloromethane 0.16 ml (2 mmol) of methanesulfonyl chloride in 2 ml of dichloromethane is added dropwise below 10 °C, and the reaction mixture is stirred at room temperature for 10 h. Then 50 ml of 8% of sodium hydrogencarbonate solution is added to the mixture, the organic layer is separated and the water phase is extracted three times with 10 ml of dichloromethane. The combined organic layers are dried over sodium sulfate, concentrated, the residue is treated with diethylether and the crystals are filtered to yield 0.25 g (30 %) of the title compound. Mp.: 128-130 °C (diethylether)

Example 18

2-(4-Benzylpiperidine-1-yl)-N-(3-hydroxyphenyl)-2-oxoacetamide (45 70001991)

The title compound is prepared from (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8b) and 3-aminophenol (Aldrich) according to the method described in Example 2. Mp.: 158-160 °C (water)

Example 19

N-(3-Cyanophenyl)-2-[4-(4-fluorobenzyl)piperidine-1-yl)-2-oxoacetamide (45 70002057)

The title compound is prepared from [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid (Example 1b) and 3-aminobenzonitrile (Aldrich) according to the method described in Example 1c. Mp.: 135-138 °C (diethylether)

Example 20

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(3-methylsulfonylaminophenyl)-2-oxoacetamide (45 70002081)

20a) 2-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(3-nitrophenyl)-2-oxoacetamide (45 70001964)

The title compound is prepared from 4-(4-fluorobenzyl)piperidine and N-(3-nitrophenyl)oxalamic acid (Example 17a) according to the method described in Example 2. Mp.: 135-138 °C (diethylether)

20b) N-(3-Aminophenyl)-2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxoacetamide (45 70002019)

The title compound is prepared from 2-[4-(4-fluorobenzyl)piperidine-1-yl]-N-(3-nitrophenyl)-2-oxoacetamide according to the method described in Example 17c. Mp.: 117-120 °C (diethylether)

20c) 2-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(3-methylsulfonylaminophenyl)-2-oxoacetamide

The title compound is prepared from N-(3-aminophenyl)-2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxoacetamide according to the method described in Example 17d. Mp.: 102-106 °C (diethylether)

Example 21

2-(4-Benzylpiperidine-1-yl)-N-(4-hydroxyphenyl)-2-oxoacetamide (45 70002117)

The title compound is prepared from (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8b) and 4-aminophenol (Aldrich) according to the method described in Example 1c. Mp.: 72-75 °C (diethylether)

Example 22

2-(4-Benzylpiperidine-1-yl)-N-(4-methanesulfonylaminophenyl)-2-oxoacetamide (45 70002123)

The title compound is prepared from (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8b) and N-(4-aminophenyl)methanesulfonamide [Tetrahedron, **42,** 5739. (1986)] according to the method described in Example 2. Mp.: 221-225 °C (water)

Example 23

1-(4-Benzylpiperidine-1-yl)-N-(1H-indazol-5-yl)-2-oxoacetamide (45 70001814)

The title compound is prepared from 5-aminoindazol (Aldrich) and (4-benzyl-piperidine-1-yl)oxoacetic acid (Example 8b) according to the method described in Example 1c Mp.: 204-209 °C (diethylether)

Example 24

1-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(1H-indazol-5-yl)-2-oxoacetamide (45 70001816)

The title compound is prepared from 5-aminoindazol (Aldrich) and [4-(4-fluorobenzyl)-piperidine-1-yl]oxoacetic acid (Example 1b) according to the method described in Example 2. Mp.: 198-200 °C (diethylether)

Example 25

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-yl) acetamide (45 70001818)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazine-3-one [J. Med. Chem., **32,** 1627. (1989)] and [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid (Example 1b) according to the method described in Example 2. Mp.: 209-212 °C (diethylether).

Example 26

N-(1H-Benzimidazol-5-yl)-2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxoacetamide (45 70001820)

The title compound is prepared from (1H-benzimidazol-5yl)amine [Synth. Commun., **29,** 2435. (1999)] and [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid Example 1b) according to the method described in Example 1c. Mp.: 104-110 °C (diethylether).

Example 27

1-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-(1H-indazol-5-ylamino)ethanone (45 70001843)

The title compound is prepared from 5-aminoindazol (Aldrich) and 2-chloro-1-[4-(4-fluorobenzyl)piperidine-1-yl]ethanone (Example 14a) according to the method described in Example 4. Mp.: 113-114 °C (diethylether)

Example 28

2-(4-Benzylpiperidine-1-yl)-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-yl)-acetamide (45 70001844)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazine-3-one [J. Med. Chem., **32,** 1627. (1989)] and (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8b) according to the method described in Example 2. Mp.: 123-126 °C (diethylether)

Example 29

2-(4-Benzylpiperidine-1-yl]-N-(1H-indazol-5-yl)acetamide (45 70001894)

a) 2-Chloro-N-(1H-indazol-5-yl)acetamide

The title compound is prepared from 5-aminoindazol (Aldrich) and chloroacetyl chloride according to the method described in Example 4a. Mp.: 175-178 °C (diethylether)

b) 2-(4-Benzyl-piperidine-1-yl]-N-(1H-indazol-5-yl)acetamide

The title compound is prepared from 2-chloro-N-(1H-indazol-5-yl)acetamide and 4-benzylpiperidine (Aldrich) according to the method described in Example 4. Mp.: 170-174 °C (diethylether)

Example 30

1-(4-Benzylpiperidine-1-yl)-2-(1H-indazol-5-yl)aminoethanone (45 70001949)

30a) 2-Chloro-1-(4-benzylpiperidine-1-yl)ethanone

The title compound is prepared from 4-benzylpiperidine and chloroacetyl chloride according to the method described in Example 4a. Mp.: 42-47 °C

30b) 1-(4-benzylpiperidine-1-yl)-2-(1H-indazol-5-yl)aminoethanone

The title compound is prepared from 5-aminoindazol (Aldrich) and 2-chloro-1-(4-benzylpiperidine-1-yl)ethanone according to the method described in Example 4b. Mp.: 153-155 °C (diethylether).

Example 31

2-(4-Benzylpiperidine-1-yl]-N-(1H-indazol-5-yl)acetamide (45 70002014)

The title compound is prepared from 2-chloro-N-(1H-indazol-5-yl)acetamide (Example 29a) and 4-(4-fluorobenzyl)piperidine according to the method described in Example 4b. Mp.: 149-152 °C (diethylether)

Example 32

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-ylamino)ethanone (45 70002015)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazine-3-one [J. Med. Chem., **32,** 1627. (1989)] and 2-chloro-1-[4-(4-fluorobenzyl)piperidine-1-yl]-ethanone (Example 14a) according to the method described in Example 4b. Mp.: 156-161 °C (diethylether).

Example 33

2-[4-(4-Fluorobenzyl)piperidine-1-yl]-N-(5-methyl-2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-oxoacetamide (45 70002102)

The title compound is prepared from 6-amino-5-methyl-3H-benzoxazol-2-one [DE 440097] and [4-(4-fluorobenzyl)piperidine-1-yl]oxoacetic acid according to the method described in Example 1c. Mp.: 189-192.5 °C (diethylether).

Example 34

2-(4-Benzylpiperidine-1-yl)-N-(5-methyl-2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-oxo-acetamide (45 70002103)

The title compound is prepared from 6-amino-5-methyl-3H-benzoxazol-2-one [DE 440097] and (4-benzylpiperidine-1-yl)oxoacetic acid (Example 8b) according to the method described in Example 1c. Mp.: 195-196 °C (diethylether).

Example 35

2-(4-Benzylpiperidine-1-yl)-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-ylamino)-ethanone (45 70002104)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazine-3-one [J. Med. Chem., **32,** 1627-30 (1989)] and 2-chloro-1-(4-benzylpiperidine-1-yl)ethanone (Example 30a) according to the method described in Example 4.b. Mp.: 172-175 °C (diethylether).

Example 36

Preparation of pharmaceutical compositions:

a) Tablets:

0.01-50 % of active ingredient of formula I, 15-50 % of lactose, 15-50 % of potato starch, 5-15 % of polyvinyl pyrrolidone, 1-5 % of talc, 0.01-3 % of magnesium stearate, 1-3 % of colloid silicon dioxide and 2-7 % of ultraamylopectin are mixed, then are granulated by wet granulation and pressed to tablets.

b) Dragées, filmcoated tablets:

The tablets made according to the method described above are coated by a layer consisting of entero- or gastrosolvent film, or of sugar and talc. The dragées are polished by a mixture of beeswax and carnuba wax.

c) Capsules:

0.01-50 % of active ingredient of formula I, 1-5 % of sodium lauryl sulfate, 15-50 % of starch, 15-50 % of lactose, 1-3 % of colloid silicon dioxide and 0.01-3 % of magnesium stearate are thoroughly mixed, the mixture is passed through a sieve and filled in hard gelatin capsules.

d) Suspensions:

Ingredients: 0.01-15 % of active ingredient of formula I, 0.1-2 % of sodium hydroxide, 0.1-3 % of citric acid, 0.05-0.2 % of nipagin (sodium methyl 4-hydroxybenzoate), 0.005-0.02 % of nipasol, 0.01-0.5 % of carbopol (polyacrilic acid), 0.1-5 % of 96 % ethanol, 0.1-1 % of flavoring agent, 20-70 % of sorbitol (70 % aqueous solution) and 30-50 % of distilled water.

To solution of nipagin and citric acid in 20 ml of distilled water, carbopol is added in small portions under vigorous stirring, and the solution is left to stand for 10-12 h. Then the sodium hydroxide in 1 ml of distilled water, the aqueous solution of sorbitol and finally the ethanolic raspberry flavor are added with stirring. To this carrier the active ingredient is added in

small portions and suspended with an immersing homogenizator. Finally the suspension is filled up to the desired final volume with distilled water and the suspension syrup is passed through a colloid milling equipment.

e) Suppositories:

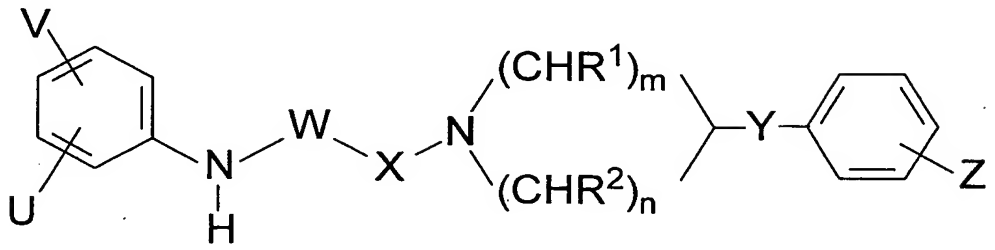
For each suppository 0.01-15% of active ingredient of formula I and 1-20% of lactose are thoroughly mixed, then 50-95% of adeps pro suppository (for example Witepsol 4) is melted, cooled to 35 °C and the mixture of active ingredient and lactose is mixed in it with homogenizator. The obtained mixture is mould in cooled forms.

f) Lyophilized powder ampoule compositions:

A 5 % solution of mannitol or lactose is made with bidistilled water for injection use, and the solution is filtered so as to have sterile solution. A 0.01-5 % solution of the active ingredient of formula I is also made with bidistilled water for injection use, and this solution is filtered so as to have sterile solution. These two solutions are mixed under aseptic conditions, filled in 1 ml portions into ampoules, the content of the ampoules is lyophilized, and the ampoules are sealed under nitrogen. The contents of the ampoules are dissolved in sterile water or 0.9 % (physiological) sterile aquequs sodium chloride solution before administration.

What we claim is:

1. New carboxylic acid amide derivatives of formula (I)



(I)

- wherein

V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C_1-C_4 alkylamino optionally substituted by a halogen atom or halogen atoms , arylamino optionally substituted by a halogen atom or halogen atoms , aralkylamino optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C_1-C_4 alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C_1-C_4 alkyl-SO_2-NH-CH_2-, NH_2-$(CH_2)_{1-4}$-SO_2-NH-, NH_2-$(CH_2)_{1-4}$-(CO)-NH-, sulfamoyl [NH_2-SO_2-], formyl [-CHO], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, halogenmethyl, tetrazolyl group, or C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkanoyloxy, phenyl or C_1-C_4 alkoxy groups, optionally substituted by amino group, or

the neighboring V and U groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form a 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

W and X independently are carbonyl, methylene, -C(=NOH)-, -C(=NH)-, -CH(alkyl)- group - wherein alkyl is a C_1-C_4 alkyl group - with the restriction, that the meaning of W and X can not be methylene at the same time

Y is oxygen atom, as well as C_1-C_4 alkylene, C_1-C_4 alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)- , $-CH_2O-$, -CH(OH)-, $-OCH_2-$ group, - wherein alkyl is a C_1-C_4 alkyl group -

Z is hydrogen or halogen atom, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R^1 and R^2 independently are hydrogen atom or alkyl group, or R^1 and R^2 together form an optionally substituted C_1-C_3 bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time,

and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases with the proviso that

when Z means hydrogen atom, Y means $-CH_2-$ group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, W means -CO- group, X means $-CH_2-$ group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means $-CH_2-$ group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, both of W and X mean -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxycarbonyl substituent.

2. One compound of the following group of carboxylic acid amide derivatives belonging to the scope of claim 1

2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide,

2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide,

2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)acetamide,

2-[4-(4-fluorobenzyl)piperidine-1-yl]-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)acetamide,

2-(4-benzylpiperidine-1-yl)-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide,

2-[4-(4-fluorobenzyl)piperidine-1-yl]-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide,

2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-5-yl)acetamide,

2-(4-benzyl)piperidine-1-yl]-N-(4-cyanophenyl)-2-oxoacetamide,

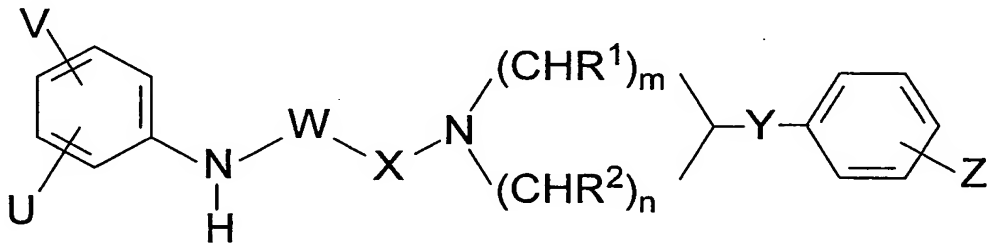
2-(4-benzylpiperidine-1-yl)-N-(4-cyanophenyl)acetamide,

2-(4-benzylpiperidine-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)acetamide,
2-(4-benzylpiperidine-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide,
2-(4-benzylpiperidine-1-yl)-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)acetamide,
2-(4-benzylpiperidine-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)acetamide,
5-{2-[4-(4-fluorobenzyl)piperidine-1-il]-2-oxoethylamino}-1,3-dihydro-benzimidazol-2-one,
6-{2-[4-(4-fluorobenzyl)piperidine-1-il]-2-oxoethylamino}-3H-benzoxazol-2-one,
N-(4-cyanophenyl)-2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxoacetamide,
2-(4-benzylpiperidine-1-yl)-N-(3-methylsulfonylaminophenyl)-2-oxoacetamide,
2-(4-benzylpiperidine-1-yl)-N-(3-hydroxyphenyl)-2-oxoacetamide,
N-(3-cyanophenyl)-2-[4-(4-fluorobenzyl)piperidine-1-yl)-2-oxoacetamide,
2-[4-(4-fluorobenzyl)piperidine-1-yl]-N-(3-methylsulfonylaminophenyl)-2-oxoacetamide,
2-(4-benzylpiperidine-1-yl)-N-(4-hydroxyphenyl)-2-oxoacetamide,
2-(4-benzylpiperidine-1-yl)-N-(4-methanesulfonylaminophenyl)-2-oxoacetamide,
1-(4-benzylpiperidine-1-yl)-N-(1H-indazol-5-yl)-2-oxoacetamide,
1-[4-(4-fluorobenzyl)piperidine-1-yl]-N-(1H-indazol-5-yl)-2-oxoacetamide,
2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-yl)-acetamide,
N-(1H-benzimidazol-5-yl)-2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-oxoacetamide,
1-[4-(4-fluorobenzyl)piperidine-1-yl]-2-(1H-indazol-5-ylamino)ethanone,
2-(4-benzylpiperidine-1-yl)-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-yl)-acetamide,
2-(4-benzylpiperidine-1-yl]-N-(1H-indazol-5-yl)acetamide,
1-(4-benzylpiperidine-1-yl)-2-(1H-indazol-5-yl)aminoethanone,
2-(4-benzylpiperidine-1-yl]-N-(1H-indazol-5-yl)acetamide,
2-[4-(4-fluorobenzyl)piperidine-1-yl]-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-ylamino)ethanone,
2-[4-(4-fluorobenzyl)piperidine-1-yl]-N-(5-methyl-2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-oxoacetamide,
2-(4-benzylpiperidine-1-yl)-N-(5-methyl-2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-oxoacetamide,
2-(4-benzylpiperidine-1-yl)-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-ylamino)ethanone,
and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases.

3. Pharmaceutical compositions having an NR2B subtype specific NMDA antagonist effect, **characterized by** comprising a biologically effective dose of a

carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, V, U, W, X, Y, Z , m and n are as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases as active ingredient and carriers, filling materials and the like usually applied in pharmaceuticals.

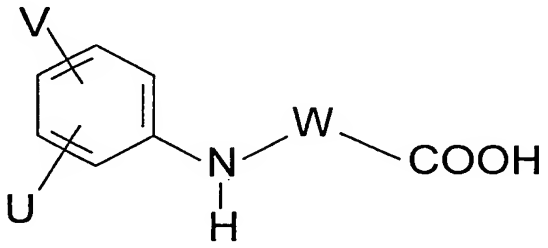
4. Process for the synthesis of carboxylic acid amide derivatives of formula (I),



(I)

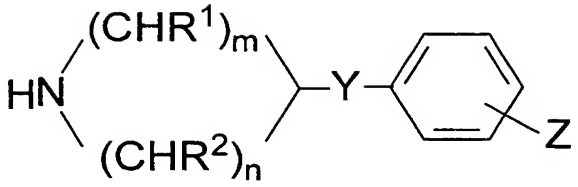
– wherein the meaning of R^1, R^2, V, U, W, X, Y, Z , m and n are as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases as active ingredient, **c h a r a c e r i z e d b y**

a.) for producing of compounds of formula (I) having -CO- group in place of X - wherein the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (I) - a carboxylic acid of formula (II)



(II)

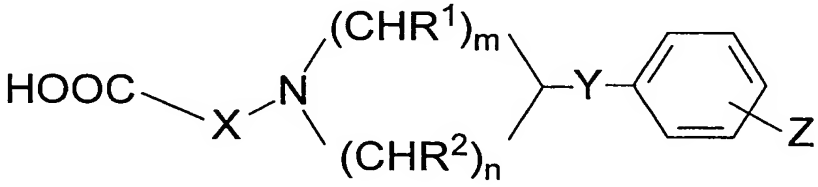
- wherein the meaning of U, V and W are as given for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (III)



(III)

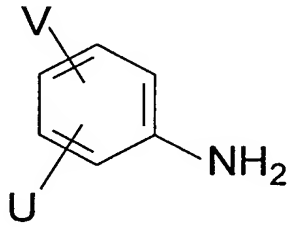
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (I) - , or

b.) for producing of compounds of formula (I) having -CO- group in place of W - wherein the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) - a carboxylic acid of formula (IV)



(IV)

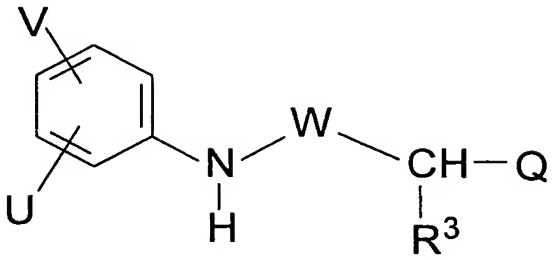
- wherein the meaning of X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (V)



(V)

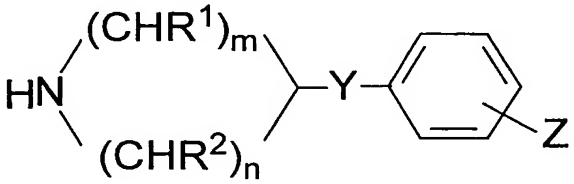
- wherein the meaning of U and V are as given before for the formula of (I) -, or

c.) for producing of compounds of formula (I) having $-CH_2-$ or -CH(-alkyl)- group in place of X - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VI)



(VI)

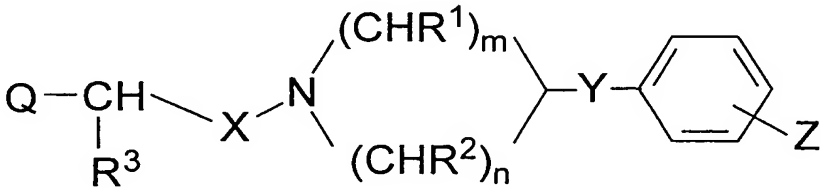
- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and U, V and W are as described above for the formula of (I) - is reacted with an amine of formula (III)



(III)

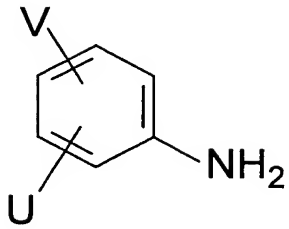
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (I) -, or

d.) for producing of compounds of formula (I) having $-CH_2-$ or -CH(-alkyl)- group in place of W - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VII)



(VII)

- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - is reacted with an amine of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) -,

and the obtained compounds of formula (I) - where R^1, R^2, Y, Z, U, V, X, W, n and m are as defined above - in given case are transformed into an other compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (I) can be transformed into a salt by treatment with a base and/or are resolved into their optical antipodes.

5. Process for manufacturing pharmaceutical compositions having NR2B selective NMDA receptor antagonist effect, **characterized by** mixing a carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, V, U, W, X, Y, Z , m and n are as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases with carriers, filling materials and the like usually applied in pharmaceuticals.

6. Method of treatment and alleviation of symptoms of the following diseases of mammals – including human - traumatic injury of brain or spinal cord, human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis, tolerance and/or dependence to opioid treatment of pain, withdrawal syndromes of e.g. alcohol, opioids or cocaine, ischemic CNS disorders, chronic neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, pain and chronic pain states, such as neuropathic pain or cancer related pain, epilepsy, anxiety, depression, migraine, psychosis, muscular spasm, dementia of various origin, hypoglycemia, degenerative disorders of the retina, glaucoma, asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss **characterized by** administering effective amount/amounts of a carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, V, U, W, X, Y, Z , m and n are as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically

acceptable salts of it formed with acids or bases as such or combined with carriers, filling materials and the like usually applied in pharmaceuticals to the mammal to be treated.

RICHTER GEDEON VEGYÉSZETI GYÁR R.T.